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(54) Title: THREE-DIMENSIONAL BIOREMODELABLE COLLAGEN FABRICS

(57) Abstract

The invention is in the field of tissue engineering implantable medical devices and is directed to three-dimensional bioremodelable fabrics made from collagen threads which are used to replace or repair tissue organs. The fabrics are tailor-made to suit a wide variety of applications with varied porosity, elongation, and strength requirements based on the knowledge gained from biomimetic studies.

THREE-DIMENSIONAL BIOREMODELABLE COLLAGEN FABRICS

Field of the Invention

The invention is in the field of tissue engineering implantable medical devices and is directed to three-dimensional bioremodelable fabrics made from collagen threads which are used to replace or repair tissue or organs.

BACKGROUND OF THE INVENTION

One of the most important attributes of living organisms is their capacity for self-repair. Several mechanisms have evolved to achieve this, including wound healing, compensatory growth and epimorphic regeneration. Although all tissues and organs (with the possible exception of teeth) are capable of some degree of repair, mammals have unfortunately lost the ability to faithfully regenerate severely damaged body parts. In an attempt to overcome this deficiency, numerous synthetic devices have been developed, with the intention that the implants be biologically inert, and yet function for the lifetime of the recipient. Experience with synthetic devices, however, has shown that not only is biological inertness apparently impossible, but the interaction between a biomaterial and the surrounding living tissue can actually contribute to the long-term success of the implant.

The concept of a resorbable scaffold for tissue repair and regeneration has received considerable attention in recent years and has been attempted using both synthetic and natural resorbable polymers. Yannas et al., in U.S. Patent No. 4,060,081, fabricated implants from lyophilized sponges of collagen and glycosaminoglycans. Nyiles et al, *Trans Am. Soc. Artif. Intern. Organs,* 29:307-312 (1983), used resorbable polyesters for peripheral nerve regeneration. Li used a porous semipermeable collagen conduit for nerve regeneration as described in U.S. Patent No. 4,963,146 and he used fibers of collagen to form a resorbable prosthetic ligament as described in U.S. 5,263,984.

Collagen has long been used as a biomaterial. (Chvapil, et al., "Medical and Surgical Applications of Collagen," *International Review of Connective Tissue Research,* volume 6, pp. 1-60 (1973); Stenzel et al, "Collagen as a Biomaterial," *Annual Review of Biophysics and Bioengineering,* pp. 231-253 (1974); E.E. Sabelman, "Biology, Biotechnology and Biocompatibility of Collagen," volume 1, pp. 27-65 (19)). In these structures, the collagen has been formed into fibers, threads, membranes, gels and sponges. Despite

extensive research over the last fifty years, these reconstituted collagen structures do not possess the same mechanical properties of the connective tissue that they are attempting to mimic and, therefore, have often needed to e reinforced with synthetic materials. Thus, Chvapil and co-workers reinforced a collagen cylinder with Dacron to function as a vascular graft. (Chvapil M. and Krajicek M., *J. Surg.. Res.*, 3:358 (1963); Chvapil et al., *J. Biomed. Mat. Res.*, 3:315 (1969)). Dacron was also used to reinforce a collagen based wound dressing. (Song et al. *Surgery*, 59:576 (1966)). Collagen has also been mixed with glycol methacrylate to form a material for possible use in orthopedic surgery. (Chvapil et al., *J. Biomed. Mat. Res.*, 3:315 (1969))

Reconstituted collagen fibers were first produced in the 1940s and this technology was exploited to produce an extruded collagen suture. These collagen fibers were woven or knitted into a mesh for use in surgery. An open (leno) collagen weave formed from 4-0 suture materials was used by Adler et al. (Adler et al., "A Collagen Mesh Prosthesis for Wound Repair and Hernia Reinforcement," *Surgical Forum*, 13:29-30 (1962)). A similar material was also used by Friedman and Meltzer to repair endopelvic fascial defects. (Friedman and Meltzer, "Collagen mesh prosthesis for repair of endopelvic fascial defects," *Gynecology*, 106:430-433 (1970)).

Green and Patterson demonstrated in 1968 that an open weave of formalin tanned collagen fibers laminated between layers of fibrillar collagen dispersion could be used for pelvic floor reconstruction. (Green and Patterson, "Collagen Film Pelvic Floor Reconstruction Following Total Pelvic Exenteration," Surgery, Gynecology & Obstetrics, pp. 309-314 (February 1968)). A similar device was used by Jannetta and Whayne (1965) as a dural replacement in dogs.

A device made from an open collagen mesh through which three long collagen tapes were interwoven was used by Girgis and Veenema (1965). Schonbauer and Fanta (1958) implanted a mesh made from chromic tanned catgut sutures into the abdominal and dorsal fascia of dogs. All these materials were single layers of collagen weave as can be seen in Figure 2 of Girgis and Veenema (1965) and Abb. 1 of Schonbauer and Fanta (1958).

Weslowski et al., *Surgery*, 50:91 (1963) investigated production of a compound vascular graft in which some of the monofilament yarns were replaced with catgut or reconstituted collagen suture. These researchers, however, found that this graft did not function correctly due to the fact that

the collagen material was not completely absorbed by the time of healing of the fibrous capsule.

Connective tissue derive their mechanical strength and physical character mainly from the three-dimensional assembly of long, intertwined crosslinked collagen fibrils and fibers formed from one or more of the 18 known distinct types of collagen; each of which has its own structure and properties. The same type of collagens synthesized by different tissues organizes itself into different organizational structures. Thus, in skin collagen Type I, collagen fibers form a structure whereby Type I collagen fibers are laid down at various acute angles in relation to the skin surface. In tendons and ligaments, however, most of the Type I collagen fibers are arranged with their long axis parallel to the long axis of the tissue. In cornea, the Type I collagen fibers are oriented in orthogonal layers. In cylindrical organs such as blood vessels and intestine, the collagen fibers are laid down in a cross-ply arrangement with the two arrays of fibers running diagonally in a clockwise and anti-clockwise direction. In bone, the large collagen fibers are arranged such that they best counter the loads imposed on the tissue. By utilizing collagen fibers and the technology of forming three-dimensional fabrics, this organization can be mimicked to some degree in the formation of implantable bioprostheses which are designed to act as remodellable scaffolds to promote the establishment of new tissues that maintain, restore, or improve normal biological function.

It is easier to achieve a variety of fiber orientations in three-dimensions if one is not constrained by the need to interlace fibers. (See Figure 4 of Mohamed.) This fabric lacks structural integrity as the individual fibers are not interacting and the material needs to be impregnated with a matrix in order to produce an integrated structure. This technique has been used with synthetic materials to form structures with wall thicknesses of up to 8 inches. (Mohamed, *American Scientist*, 78:530-541 (1990)).

Machines which can form three-dimensional, cylindrical, weft knits in which the two layers can be bound together have also been developed. (Williams, *Advanced Composite Engineering*, volume 2 (1987)). Warp knitting with multiple re-reinforcing yarns can be used to produce a fabric that is multi-layered. (Mohamed, *supra*.) Braiding can also be used to produce highly complex, three-dimensional shapes. (Florentine, U.S. Patent No. 4,312,261). Three-dimensional weaves have also been formed. The

fabrics can be woven with a space between the layers (core fabrics) or woven as thick dense structures as seen in Figure 8 of Mohamed, *supra*.

SUMMARY OF THE INVENTION

The inventors have combined collagen's fibrillogenic capacity with textile technologies in order to bioengineer three-dimensional bioremodelable fabrics tailor-made to suit a wide variety of applications with varied porosity, elongation, and strength requirements based on the knowledge gained from biomimetic studies. The bioremodelability of the collagen fabrics of this invention permits them to undergo biodegradation in a controlled fashion so that the production of endogenous structural collagen, vascularization, and epithelialization of the fabric by the ingrowth of host cells occurs at a rate faster than the loss of biomechanical strength of the implanted fabric due to biodegradation by host enzymes. By the time the implanted collagen fabric of this invention is resorbed by the body, endogenous host tissue is in place and capable of maintaining the integrity and normal function of the tissue.

This invention provides for the production of three-dimensional bioremodelable collagen fabrics of various configurations. These fabrics are thus bioengineered implants and devices which serve the required physical function while facilitating remodeling of the replaced or repaired tissue or organ implant.

DETAILED DESCRIPTION OF THE INVENTION

I. Tissue Engineering.

This invention is directed to three-dimensional bioremodelable fabrics formed from collagen threads. This invention is directed to implantable medical devices which can be used to replace or repair tissue or organs. More particularly, this invention is directed to devices that can serve as in vivo scaffolds for the regeneration of new tissue. In the textile industry, three-dimensional fabrics achieve their greatest strength when the threads are intertwined, interlaced or intermeshed in the crosswise, lengthwise and thickness directions. These directions are also termed the X-, Y-, and Z-axes. The three-dimensional bioremodelable fabrics of this invention are applications of textile techniques with knowledge of collagen's fibrillogenic capacity and ability to bioremodel. The three-dimensional bioremodelable

fabrics are made from collagen threads and, using textile techniques, are woven and/or knitted into the desired configurations to replace or repair organs and tissues.

The three-dimensional fabrics of this invention are meant to include collagen threads in multiaxial directions, as compared with two-dimensional fabrics, which only have width and length directions. A two-dimensional fabric does, of course, have some depth based on the diameter of the threads used in the construction, but it is not a true multiaxial, three-dimensional fabric.

As used herein "fabric" means a structure used as the three-dimensional framework or scaffold for bioremodeling which can be formed into a number of patterns or shapes, as dictated by the biomimetics approach to tissue engineering. Thus, for example, as explained in more detail below, a three-dimensional bioremodelable fabric can be shaped into a structure resembling a bone, with a hollow core. Additionally, the collagen threads can be formed into a solid configuration, such as a structure resembling a sling for hernia repair. The term "fabric" is used because it describes a construct made from collagen threads using textile techniques. Thus, for example, the term is meant to include braids that can be made into a wide range of geometric shapes in which the braiding threads interlock the entire structure.

Several types of structures are described in detail in co-pending application, U.S. serial number 08/216,527, filed concurrently herewith as "Biocompatible Devices," the contents of which are incorporated herein by reference in its entirety.

The bioremodelable collagen fabric is designed not only to perform an immediate physical function, but equally importantly, to guide and encourage appropriate host tissue formation, dissolve, and gradually transfer the load to the newly formed collagen. "Bioremodelable" means the ability of the implanted collagen fabric to function as a scaffold for new host tissue ingrowth by facilitating the production of endogenous structural collagen, vascularization, and epithelialization by the ingrowth of host cells at a rate faster than the loss of biomechanical strength of the implanted fabric due to biodegradation. As the bioremodelable fabric biodegrades, new tissue forms, thus creating a permanent functional analog of the original tissue or organ.

A three-dimensional fabric is a woven and/or knitted product which is multiaxial, with X-, Y-, and Z-axes. Typically, the three-dimensional fabrics

are continuously formed by intertwining a plurality of strands together, some of which are at an angle from the traditional flat fabric weaving plan. An inherent disadvantage of fiber constructs made into two-dimensional fabric sheets is their limited strength. Two dimensional fabrics are anistropic, exhibiting unequal strength properties when measured along the X- and Y-axis. To extend the use and value of textile technology into bioremodelable collagen constructs, strength in more than two directions is required. The three-dimensional fabrics of this invention can be constructed from collagen threads using textile techniques.

Three-dimensional fabric formation in the textile industry has been used to produce a number of different articles. These techniques are described in detail in the following patents, which is not intended to be limiting: U.S. Patent Nos. 5,019,435; 4917,756; 4,863,660; 4,848,414; 4,834,144; 4,805,422; 4,805,421; 4,779,429; 4,346,741; 5,067,525; 4,936,186; 4,881,444; 4,800,796; 4,719,837; 4,615,256; 4,312,261, all of which are incorporated herein by reference.

The construction of three-dimensional bioremodelable fabrics can be accomplished using the textile techniques of weaving and knitting. Using these techniques, the three-dimensional bioremodelable fabrics of this invention can be made into any of a variety of shapes: (1) a solid weave; (2) an open weave; (3) a solid knit; and (4) an open knit. All of these fabrics can be made with the same size threads or with different size threads in the same construct. Further, the threads may first be plied, braided, or otherwise manipulated to increase the diameter or strength of the threads, such as by crosslinking, prior to using them in the construction of the bioremodelable fabrics. Additionally, a combination of knit construction and weave construction can be used in the same fabric construct. These collagen fabrics may be used for a wide variety of applications with varied porosity, elongation, and strength requirements.

II. Construction of Three-Dimensional Fabrics

A. Weaving.

A woven fabric is defined in textile terms as a cloth made by interlacing or intertwining warp strands with filling strands, the woof. A warp is a series of strands extended lengthwise in a loom and crossed by the woof, the filling strands.

Multilayer woven fabrics are composed of several series of warp and filling strands that form distinct layers, one above the other. The fabrics can be woven with a space between layers (core fabrics) or woven as thick, dense structures. The layers can be bound together by interlacing warp ends in the structure with the filling of adjacent layers (angle interlock) or by having the ends interlace between the face and back layers (warp interlock). The binding yarns may also interlace vertically between layers, producing an orthogonal weave.

Multilayer woven fabrics do not need not be interlaced throughout the fabric: the addition of vertical yarns interlaced with the top and bottom horizontal yarns provides the same kind of reinforcement in a three-dimensional structure that is provided by the over and under interlacing of yarns in flat weaving.

Multilayer structures can be given additional strength by inserting in each layer stuffing yarns, which remain straight and contribute their full strength in the direction in which they are oriented. Yarns that interlace between layers as binding yarns contribute partially to the strength of their direction; in orthogonal woven fabrics, they contribute immensely to the strength in the thickness direction. There are trade-offs that must be made, however, since only one yarn can occupy any position within the structure. An increase in the fiber volume fraction (the fraction of the total volume occupied by fiber) in one direction can be achieved only at the expense of one or both of the other directions.

Most commonly, shuttle looms are used and the warp yarns are taken from a creel; since the warp is coming from many individual bobbins, it can be taken from different sources, an arrangement which allows yarns to be mixed and allows flexibility in the rates at which they are fed.

Traditional weaving machines adapt well to making multilayer panels in this way, but the complexities of creating other three-dimensional textile structures require special considerations, including maintaining consistency in yarn tension.

A key step in assuring the strength of the finished structure occurs each time the needles cross the warp. A vertical needle, threaded with the yarn that will secure the selvage loops on the vertical edge, is inserted from below the weaving area, coming up to catch the filling yarn that has just been brought across the warp. This selvage needle holds a loop of each filling yarn

at the edge of the warp as the filling needles return to their original positions. Thus a double length of filling is inserted with each cycle. The selvage needles retract for the next step, but the selvage yarn - which now holds the filling loops - is clasped and held in its vertical position by a knitting needle. To form a finished corner edge, the loops of selvage yarns are knitted together as the process continues.

The step that is called "beat-up" in traditional weaving is used in three-dimensional weaving to position the vertical (z) yarns. These yarns are threaded through needles suspended from harness frames (similar to those used in the traditional loom) and are passed through the vertical openings in a reed at angles, crossing on the opposite side of the filling needles. Once every cycle, as the z yarns are suspended in diagonal position, the reed moves horizontally to push the filling against the already-woven length of textile. This action pushes the crossed z yarns into a vertical arrangement. The harnesses holding the z yarns then move up and down to reverse the positions of the yarns before the process begins again. In this way the vertical yarn that has just been stretched from the bottom to the top of the textile is passed over the topmost filling yarn and held in position to be placed in the opposite direction at the next stage of the weaving.

With additional harness frames and devices for dobby or Jacquard weaving, it is possible to weave many structures.

It is also possible to vary the fiber volume fraction to give the composite the ability to withstand extra stresses in a particular direction. Since in this system the filling yarn is inserted in the form of a doubled loop, a balanced structure is achieved when the filling yarns are half the size of the warp and z yarns. One can keep the structure balanced in this way but vary the sizes of the yarns used in each of the three directions. In addition, the fiber volume fraction can be varied in the vertical direction by using more than one warp yarn for every z yarn. This proportion may not be required for every application.

B. Knitting.

A knitted fabric is formed by interlacing yarn or thread in a series of connected loops. The knit stitch is a basic knitting stitch usually made with yarn at the back of the work by inserting the right needle into the front part of the loop on the left needle from the left side, catching the yarn with the point

of the right needle, and bringing it through the first loop to form a new loop. The purl stitch a knitting stitch usually made with the yarn at the front of the work by inserting the right needle into the front of a loop on the left needle from the right, catching the yarn with the right needle, and bringing it through to form a new loop.

Knitting is a versatile technique for producing strong, porous structures and is the preferred method of making the three-dimensional bioremodelable collagen fabrics. The main advantage of knitting over weaving is that knitting introduces closed loops at the yarn crossover points, allowing the product to hold sutures with very little bite, and without needing to fold the material at the suture line. In contrast, weaving interposes parallel yarns, resulting in a fabric more subject to fraying when cut. In addition, knitting offers more options for varying the physical character of the final material than weaving does.

There are two basic types of knitting machines. Weft knitting machines use only a single end of yarn and individual needles cast off stitches sequentially. Warp knitting machines use many ends of yarn parallel-wound on a cylinder (the warp) and man needles (a "needle bar") cast off stitches simultaneously to produce the fabric.

Warp knitting, however, offers distinct advantages. Since weft knitted fabrics are formed from a single end, they can unravel if that end is pulled, or if the fabric is cut in the middle and the free end is pulled. Most warp knitted fabrics do not unravel when cut. Moreover, by simultaneously using additional warps and additional needle bars, complex fabrics can be designed in which a heavier weight, and more complex fabric with new mechanical properties results.

There are two main categories of warp knitting machines. The Raschel type has a latched needle to hold the yarn. The Tricot type holds the yarn with flexible bent tip, termed a "beard." Raschel machines offer a more versatile array of knitting patterns, but Tricot machines exert less stress on the fibers. Both flat and tubular structures can be made on Raschel machines; Tricot machines are mainly used to produce flat structures. Collagen fabrics can be made by both flat and tubular weft knitting, and both Raschel and Tricot warp knitting. The variety of knitting designs runs the gamut from open elastic meshes, to dense stable fabrics, to tubular structures, using

starting materials from individual or multiple monofilament threads to twisted or braided yarns.

Variations of knitting techniques can be used to manufacture three-dimensional constructs in cylindrical or conical shapes. In this approach, axial rods are placed to form the shape of the structure; after radial yarns are added, knitting needles catch the radial yarns and create chain stitches to loop these yarns around the axial rods, which are replaced with axial reinforcing fibers when the preform is pulled off the machine.

C. Braiding.

Braiding techniques have been developed to produce complex shapes (Florentine 1982). In essence, these are multilayered structures in which some braiding yarns traverse the inner layers to bind the two exterior layers together. Complex shapes can be formed by braiding over a removable mandrel whereby the contours of the final braid match those of the mandrel as can be seen in Figure 7 of Mohamed, *supra*.

III. Collagen Threads

The collagen that can be used in this invention can be formed from collagen parts derived from animals, or from collagen produced by cells in tissue culture. Collagen can be extracted in a number of ways from animal parts. Suitable sources of collagen include, but are not limited to, skin, tendons, bone, cartilage, ligaments, fascia, intestinal submucosa, placenta. Extraction methods that have been commercialized for the production of collagen preparations can be divided into the categories of dispersion, digestion, and dissolution.

Dispersion techniques generally involve swelling and comminution of connective tissue. This results in heterogeneous material with a high solids content formed from portions of collagen fibrils. Digestion utilizes proteolytic enzymes which cleave the telopeptides downstream of the crosslinks. This method produces a monomeric solution of partially degraded collagen which, although still contain intact triple helical regions, has now lost most or all of the telopeptide region. The dissolution of collagen relies on the acid labile nature of the newly formed covalent cross linkages. This technique, which employs low pH solutions, results in extraction of the intact, collagen molecule. Although yields are relatively low compared to the

enzymatic digestion methods, there are major benefits to this technique due to the fact that the complete, native structure is maintained.

Various types of collagen threads can be used in this invention. Different types of collagen threads are described in a number of patents, for example, Silver, U.S. Patent No. 5,171,273; Shu Tun Li, U.S. Patent No. 5,263,984; PCT application WO93/06791 and co-pending patent application, U.S. serial no. 08/216,527, "Biocompatible Devices," all of which are incorporated herein by reference. Collagen sutures are also included in the definition of collagen threads and can be used in this invention. Collagen sutures are described in U.S. Patent Nos. 3,114,593 and 3,114,591, incorporated herein by reference.

Thread size can be measured two ways. The diameter can be measured microscopically (10X) using a measuring eyepiece, averaging the readings taken on at least five thread samples in at least five random locations. Another way to measure diameter, which is more characteristic of textile fibers, is to measure thread mass per length, or denier (mass in grams per 9000 meters of length). For use in this invention, the denier can range from about 15 to about 300, typically about 80.

Thread strength can be determined by mounting a 50 mm sample lengths in a force gauge (Chatillon Corp., Agawam, Massachusetts) and pulling at 50% strain per minute until failure. Ultimate elongation and load at break can then be characterized.

Thread knitability may be evaluated by knitting a 5 mm diameter tubular fabric on a circular (weft) knitting machine (Lamb, Chicopee, MA).

Shrinkage temperature, a measure of the stability of the collagen triple helix, can be measured by immersing a 5 to 7 loop of thread loaded with 2.5 g in 1.0 mM potassium phosphate monobasic, 11 mM sodium phosphate dibasic, and 150 mM NaCl at pH 7.30, and heating at 1°C per minute until shrinkage occurs. The temperature at which the sample shrinks by at least 10% is the shrinkage temperature.

IV. Uses of Three-Dimensional Bioremodelable Fabrics

The three-dimensional bioremodelable collagen fabrics of this invention have many uses as organ implants or in tissue repair or replacement.

Bioremodelable collagen constructs can be braided or bundled for use as load bearing orthopedic prostheses such as bone, cartilage, tendon or ligament replacements. When used as a bone prosthesis, the collagen constructs can be shaped into a structure with a hollow core. Alternatively, the bone prosthesis can be formed of (1) an outer, hollow tubular structure with the desired strength and biomechanical properties required to bear the load exerted on the particular bone being replaced and the necessary diameter required to achieve a suitable match at the site of implantation and (2) an inner matrix of collagen fabric of the desired porosity to permit it to be seeded with hematopoietic stem cells.

Collagen fabric knitted or woven into tubular form may also be used as a support for a vascular prosthesis, providing that a luminal smooth flow surface is also provided. Similarly, tubes of larger diameter could be woven for use as implants in the reconstructive-restorative surgery of tubular organs such as the larynx, trachea, bronchi, esophagus, urethra, intestine, colon or bile ducts.

Collagen fabric constructs may also be formed in the shape of a wedge for implantation in synovial joints to replace a damaged articular miniscus or in the shape of a disk to replace damaged intervertebral disks. The implants will be bioremodeled with endogenous fibrocartilage to create a new miniscus or disk.

The collagen fabric constructs of this invention can also be sprayed or coated with antibiotics, antiviral agents, growth factors, thrombosis-resistant agents or the like before implantation to enhance remodeling or to prevent infection.

The collagen fabric could also be produced from collagen threads that have been formed from a mixture of collagen and one or more of the following:

(a) Proteoglycans or other extra-cellular matrix components such as fibronectin, laminin, tenascin;

(b) Cytokines such as members of the transforming growth factor betas (TGFbs), platelet derived growth factor (PDGF), insulin like growth factors (IGFs), fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs) or interleukin (IL) families. These factors could be uniformly incorporated within the collagen thread or coextruded such that a gradient of factor was formed from the center to the edge of the thread.

(c) Antiviral, antibacterial or anti-fungal agents.

The collagen fabric could also be produced from non crosslinked collagen and implanted in this state. The collagen fabric may also be crosslinked by any of the known crosslinking agents described in U.S. Patent No. 5,263,984, Column 3, lines 54-62. Moreover, the individual threads could be crosslinked prior to formation of the construct so that in order to control the biomechanical properties of and cell response to the construct the fabric could be made from mixtures of crosslinked and non crosslinked threads.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

Formation of an Abdominal Wall Repair System

This fabric was manufactured first by producing a 2-ply collagen yarn. Collagen threads were made by the process described in copending patent application, U.S. serial number 08/216,527, filed concurrently herewith, as "Biocompatible Devices." Two monofilament strands of thread were each twisted at 1.5 twists-per-inch (tpi) in the Z-direction; then, they were twisted together at 2.5 tpi in the S-direction. The result was a 2-ply yarn which does not unravel or spring. This yarn was then warped using a conventional single and warper (more convenient for trial quantities than a creel) onto an ordinary knitting beam. The hernia repair fabric under investigation used three such beams on a 20-gauge Tricot sample knitting machine in a pattern designed for high bulk and low extensibility. The stitch design is as follows:

- Front bar (#1): 0-1/1-0//
- Middle bar (#2): 1-0/4-5//
- Back bar (#3): 4-5/1-0//

This fabric was evaluated as an abdominal wall replacement in the rat model, using a full muscle layer defect measuring 2 cm by 2 cm. Before implantation, the fabric was cleaned with acetone, crosslinked with 50 mM EDC in 90% acetone at room temperature overnight, depyrogenated in 0.1 N NaOH at 4°C overnight, and cold chemical sterilized. The fabric could also be sterilized (dry) by gamma irradiation or ethylene oxide.

In this study, collagen fabric was examined for its ability to close a full-thickness abdominal excision in a rat model. A 2 cm x 2 cm full-thickness abdominal wall defect was created in each of 5 Sprague-Dawley rats. A 2.5 cm

x 2.5 cm piece of collagen fabric was sutured over the defect using six 4-0 polypropylene, with a 0.25 cm overlap around the perimeter. Additional continuous sutures were placed around the fabric perimeter, through the fabric and muscle. At timepoints of 3 weeks and 12 weeks. the animals were examined for herniation and mechanical stability of the implant. The implants, along with a margin of surrounding tissue, were then removed and fixed for histological processing as described below. The area of the repair was assessed by tracing the perimeter of the wound.

All animals were healthy for the duration of the experiment. No abdominal herniation was observed up to 12 weeks postimplantation. On visual inspection at 3 weeks, the fabric was a dark-pink color, suggesting good neovascularization. Blood supply to the tissue within the fabric was provided from a single small projection of the omen-turn (about 2 mm wide) to the underside of the fabric. No visceral adhesions were noted. Histology at 3 weeks showed a vigorous cellular infiltrate, with numerous fibroblasts and some macrophages. Abundant matrix deposition could be seen in the interstices of the fabric.

This fabric has high bulk and thickness with low extensibility, and would be useful for space-filling applications with moderate load-bearing requirements. Further, several layers of 3-dimensional fabric could be thus joined to provide compound fabric of any thickness desired.

EXAMPLE 2

Formation of a Menisci Repair Device for Knees

When the knee bends, the menisci stretch to accommodate the movement. When the knee bends and twists, the menisci may overstretch and tear. The medial meniscus is especially vulnerable to tearing because it is anchored to the tibial collateral ligament, and so has less mobility than the lateral meniscus. The lateral or medial meniscus can be repaired using the menisci repair device of this invention.

To form the menisci repair device, the knitted fabric described in Example 1 above, is rolled by laying the fabric on a flat surface, and taking the length of one side of the fabric and rolling it end over end. The fabric is rolled to approximate the overall length and diameter of meniscus to be repaired. The rolled menisci repair device is then curled to conform to the original contours of the meniscus.

The rolled menisci repair device is then crosslinked with standard techniques using 50mM 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) for 8 hours in 90% acetone, then rinsing exhaustively with water. Before implantation, the device is depyrogenated by soaking in 0.1M NaOH overnight at 4°C, and sterilized by room temperature ethylene oxide (EtO) treatment.

The device is implanted into the lateral or medial, or both, meniscus surrounding the kneecap.

EXAMPLE 3

Formation of Tubular Structures for Bone Repair

Fabric constructs with hollow structures are also produced by direct tubular knitting. The yarn described in Example 1 above is Raschel knitted with two needle bars into a tube using the following pattern:

- Front bar: 1-0/1-2
- Back bar: 1-2/1-0

A tubular fabric has its inner and outer diameter dimensions, mechanical strength and porosity determined by the specific knitting design employed. If necessary, nesting structures of progressively larger diameters may be joined to provide a hollow tube of any wall desired wall thickness. The center of the cylinder may be filled with collagen in any form, for example, a parallel bundle of collagen threads formed as described above, a paste of homogenized collagen fibers, a collagen gel. Any of the elements of the structure may be coated with various agents such as bone morphogenic proteins to stimulate bone repair. A knitted device may be attached over either end of non-union fracture in order to stimulate bone repair.

EXAMPLE 4

Formation of a Braided Tubular Structure for Bone Repair

A tubular structure may be formed from more than one coaxial layer of braided collagen such that the outer diameter of the braid matched that of the bone to be repaired. The braid may be hollow or completely filled with braided material. If a hollow braid was used, the center of the cylinder may be filled with collagen in any form, for example, with a parallel bundle of collagen threads formed as described above; a paste of homogenized collagen fibers; a collagen gel; and the like. Any of the elements of the structure may

be coated with various agents, such as bone morphogenic proteins to stimulate bone repair. A braided medical device formed in this fashion may be attached over either end of a non-union fracture to stimulate bone repair.

EXAMPLE 5

Formation of a Woven Fabric for Filling a Deep Dermal Wound

1. Collagen threads formed from any of the threads described above in the description may be used to weave the fabric.

2. Threads are woven by loading sets of bobbins with collagen thread. One set supplies the warp (lengthwise) yarns. These will be stationary during the weaving process. A harness suspends the vertical yarns at oblique angles (some from above and some from below). Two additional sets of yarns are used: "filling yarns" which are inserted from the side by two horizontal sets of needles and "selvage yarns" inserted from below by a pair of vertical needles. Two knitting needles are also positioned so that they can knit loops of selvage yarn together at the corners of the woven structure. To weave the structure the filling needles move between layers of warp and vertical yarns to inset the filling yarns in a crosswise direction. Before these needles retract, the vertical selvage needles move up to catch the filling; a horizontal bar in turn catches the selvage yarns at the top. The filling needles then retract and a pair of knitting needles clasps the selvage yarns to allow the cross bar to also retract. The reed which is a comblike device positioned in front of the harness then moves horizontally to pack the yarns into their final configuration. While this occurs, the vertical yarns are pushed from their diagonal position into a vertical alignment. At the end of each knitting cycle, the knitting needles pass the new loop of selvage yarn through the previous one and the harnesses switch to reverse the position of the vertical yarns for the next cycle.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. Three-dimensional bioremodelable fabric made from collagen threads.

2. The three-dimensional bioremodelable fabric of claim 1 wherein said fabric is woven.

3. The three-dimensional bioremodelable fabric of claim 1 wherein said fabric is knitted.

4. The three-dimensional bioremodelable fabric of claim 2 wherein said fabric is woven into a solid weave.

5. The three-dimensional bioremodelable fabric of claim 3 wherein said fabric is knitted into a solid knit.

6. The three-dimensional bioremodelable fabric of claim 2 wherein said fabric is woven into an open weave.

7. The three-dimensional bioremodelable fabric of claim 3 wherein said fabric is knitted into an open knit.

8. The fabric of any of claims 1-3 wherein said fabric is made with the same size threads.

9. The fabric of any of claims 1-3 wherein said fabric is made with different size threads.

10. The fabric of any of claims 1-3 wherein said fabric is made with a combination of the same and different size threads.

11. The three-dimensional bioremodelable fabric as in any one of claims 1-3, in which said fabric is formed into a cylinder.

12. The three-dimensional bioremodelable fabric as in claim 11, wherein said cylinder has a diameter suitable for repair or reconstruction of tubular organs selected from the group consisting of vascular prosthesis, the larynx, trachea, bronchi, esophagus, urethra, intestine, colon, or bile ducts.

13. The three-dimensional bioremodelable fabric as in any one of claims 1-3, in which said fabric is formed in the shape of a wedge for implantation in synovial joints to replace a damaged articular meniscus.

14. The three-dimensional bioremodelable fabric as in any one of claims 1-3, in which said fabric is formed in the shape of an intervertebral disk.

15. Three-dimensional bioremodelable tubular medical device made from braided collagen threads.

16. The medical device of claim 15 wherein said tube is either hollow or filled.

17. The medical device of claim 16 wherein said tube is filled with collagen in any form.

18. A tissue or organ implant made from three-dimensional bioremodelable fabric constructed of collagen threads.

19. The three-dimensional bioremodelable fabric as in any one of claims 1-18, in which said fabric further comprises antibiotics, antiviral agents, growth factors, or thrombosis-resistant agents.

20. The three-dimensional bioremodelable fabric as in any one of claims 1-18, in which said fabric further comprises the following components:

(a) proteoglycans or other extra-cellular matrix components such as fibronectin, laminin, tenascin;

(b) cytokines such as members of the transforming growth factor betas (TGFbs), platelet derived growth factor (PDGF), insulin like growth factors (IGFs), fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs) or interleukin (IL) families; and,

(c) antiviral, antibacterial or anti-fungal agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03455

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61F 2/02
US CL :623/11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 623/11,16, 18, 20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS search terms; "knit? and collagen# and (thread# or filament# or fiber#) and cytokine# and proteoglycan# and (antiviral# or antibio?)"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US, A, 5,308,889 (RHEE ET AL) 03 May 1994, see the entire document.	1-12, 15, 16, and 18
X	US, A, 4,880,429 (STONE) 14 November 1989, see the entire document.	1,8-11, 13, 14, and 18
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Y		1,8-11, 13, 14, and 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 APRIL 1995	Date of mailing of the international search report 10 MAY 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PAUL PREBILIC Telephone No. (703) 308-2905

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03455

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 19 and 20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.